transmembrane component iii), one region being coded for by said first recombinant DNA construct and the other different region being coded for by said second recombinant DNA construct.

33. (Three times amended) The DNA delivery system according to claim 11 wherein the spacer region is the extracellular region of CD8, CD4 or CD28 or a fragment thereof.

35. (Three times amended) The DNA delivery system according to claim 11 wherein the spacer region is an antibody hinge region or a fragment thereof linked to the extracellular region of CD28 or a fragment thereof.

53. (amended) A DNA delivery system according to claim 11, wherein the recombinant DNA construct encodes either the light chain or the heavy chain of said CDR-grafted antibody or an antigen binding fragment of said CDR-grafted antibody, said DNA delivery system further comprising a second recombinant DNA construct comprising a promoter operably linked to a reading frame coding for a signal peptide component and the heavy chain or the light chain or said CDR-grafted antibody or an antigen binding fragment of said CDR-grafted antibody, such that upon co-expression of said first and second recombinant DNA constructs in the effector cell, the light and heavy chains of the CDR-grafted antibody or an antigen binding fragment of said CDR-grafted antibody assemble to form a binding component which binds to a cell surface antigen on a target cell.

REMARKS

Claims 11, 21-24, 28-31, 33-42, 46,47, and 53 are pending in the above referenced application and stand rejected. Claims 11, 21-24, 28, 31, 33, 35, and 53, have been amended to further clarify the subject matter of the invention. Support for the amendments is found throughout the specification and no new matter has been added. Applicants respectfully submit that this application is in condition for allowance in light of the above amendments and the following discussion.

A petition for an extension of time of three (3) months for responding to the outstanding Office Action and the appropriate fee is enclosed herewith.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Claims 11 and 31 are objected to because of informalities. Claim 11 has been amended to insert the definition of CDR and the reference to "a chimeric antibody" in part ii) has been deleted and " an antigen binding fragment thereof" has been replaced by "an antigen binding fragment of said CDR-grafted antibody". Claim 31 has been corrected so that it is dependent on claim 53, rather than claim 52.

In addition, claims 21 and 22 have been amended to delete the term "chimeric". Claims 23, 24, 28, 33 and 35 have been amended to replace "antigen binding fragment thereof" with "fragment thereof". The Examiner objected to the term "fragment thereof" in claims 11, 23, 28, 33, 35 and 53 in an Advisory Action issued 25th July 2001. The phrase "antigen binding fragment thereof" was mistakenly used to replace the phrase "fragment thereof" in all of these claims when this should only have been done in claims 11 and 53. Claim 35 has also been amended to delete the phrase "all or part" which is unnecessary in view of the reference to "a fragment thereof". Furthermore, claim 53 has been amended to delete the references to chimeric antibodies.

Claims 11, 21-24, 28-31, 33-42, 46, 47 and 53 stand rejected under 35 U.S.C. 102(e) as being anticipated or clearly anticipated by Roberts (US 5,712,149). Applicants respectfully traverse this rejection for the reasons set forth below.

Claims 11, 21-24, 28-31, 33-42, 46, 47 and 53 stand rejected under 35 U.S.C. 102(e) as being anticipated by Seed *et al.* (US 5,912,170). Applicants respectfully traverse this rejection for the reasons set forth below.

Claims 11, 21-24, 28-31, 33-38, 46, 47 and 53 stand rejected under 35 U.S.C. 102(a) as being anticipated by Capon *et al.* (WO 96/24671). Applicants respectfully traverse this rejection for the reasons set forth below.

In order to expedite allowance of this application, Applicants have amended Claim 11 to a chimeric receptor in which the binding component comprises a CDR-grafted antibody or a fragment of said CDR-grafted antibody.

It is the Examiner's position that CDR-grafted antibodies are simply the combination of two unrelated antibody sequences and has alleged that Roberts and Seed disclose chimeric receptors in which the binding component is a combination of two unrelated antibody sequences. Applicants respectfully submit that this conclusion is incorrect. Applicants respectfully submit that a CDR-grafted antibody is not "simply the combination of two unrelated antibody sequences" but relates specifically to the grafting of CDRs from a first antibody into the framework of a second antibody.

While the Roberts, Seed and Capon references each disclose chimeric receptors in which the binding component may comprise a monoclonal antibody or a fragment thereof, all the references fail to teach using a binding component comprising a CDR-grafted antibody having CDRs from a first antibody and framework regions from a second antibody, as presently claimed. The monoclonal antibodies used as a binding component in the chimeric receptors of the Roberts, Seed and Capon references do not therefore have an identical chemical structure to the CDR-grafted antibody used as a binding component in the chimeric receptors of the present invention.

Furthermore, an antigen binding fragment of a CDR-grafted antibody of the present invention will be derived from the variable region of that antibody and must inherently contain CDRs from a first antibody and framework region from a second antibody. Therefore, the antigen binding fragments of monoclonal antibodies used as binding components in the chimeric receptors of the Roberts, Seed and Capon

references do not have identical structures to the fragments CDR-grafted antibodies used as binding components in the chimeric receptors of the invention.

Thus, it is clear that the Roberts, Seed and Capon references do not disclose a chimeric receptor in which the binding component is CDR-grafted antibody or a fragment of a CDR-grafted antibody, as presently claimed. All the Examples in the current application demonstrate the effectiveness of using the CDR-grafted antibody fragments in the chimeric receptors of the present invention.

Applicants also respectfully disagree with the Examiner's statement on page 8 of the official action that the pending claims do not exclude the possibility that the cytoplasmic signalling domains of the present invention are linked in nature. The claims as originally filed explicitly recited that the cytoplasmic signalling components were "not naturally linked." However, this language was removed in the Amendment After Final at the request of the previous Examiner who considered it to be superfluous in view of the amendment of the claim to specify that the receptor was encoded by a "recombinant DNA construct." Applicants therefore respectfully submit that the claims are novel over Seed in view of the fact that, unlike in Seed, the cytoplasmic signalling components in the chimeric receptors of the repent invention are not linked in nature. However, Applicants respectfully submit that this point is moot in light of the fact that the claims are novel over Seed because the claims recite that the binding component is a CDR-grafted antibody or antigen binding fragment thereof.

The claims as presently amended are therefore clearly not anticipated by the Roberts, Seed and Capon references. Applicants respectfully request reconsideration and withdrawal of the rejections over the Roberts, Seed and Capon references.

In view of the above amendment and discussion, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited. Should the Examiner wish to discuss the above amendment made herein, the undersigned attorney would appreciate the

opportunity to do so. Thus the Examiner is hereby invited to call the undersigned, collect at the number shown below.

Respectfully submitted,

Date: December 3, 2002

BOS2_319961.1

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VERSION WITH MARKINGS TO SHOW CHANGES MADE.

In the claims:

Please amend the claims as follows:

11. (Three times amended) A DNA delivery system comprising: a recombinant DNA construct and means for delivery of said construct to an effector cell, said recombinant DNA construct coding for a chimeric receptor which binds a cell surface antigen on a target cell, wherein said recombinant DNA construct comprises a promoter operably linked to a reading frame coding for:

vi) a signal peptide component;

vii) a binding component comprising ~~a chimeric antibody,~~ a complementarity determining region (CDR)-grafted antibody or an antigen binding fragment ~~thereof~~ of said CDR-grafted antibody;

viii) a transmembrane component;

ix) two or more different cytoplasmic signalling components which are selected from the group consisting of the cytoplasmic domains of a zeta, eta or epsilon chain of the T-cell receptor, CD28, the gamma chain of a Fc receptor, a cytokine receptor, a colony stimulating factor receptor, a tyrosine kinase or an adhesion molecule, B9, MB-1, CD3 delta, CD3 gamma, CD5 or CD2, or a fragment thereof, wherein at least one of said two cytoplasmic signalling components is derived from a membrane spanning polypeptide; and optionally

x) one or more spacer regions linking any two or more of said i) to iv) components, wherein, when said chimeric receptor is expressed in the effector cell and the binding component binds the cell surface antigen on the target cell, a signal is transduced in the effector cell via the cytoplasmic signalling components.

21. (Three times amended) The DNA delivery system according to claim 11 wherein the binding component is ~~a chimeric or~~ a CDR-grafted single chain Fv fragment.

22. (Three times amended) The DNA delivery system according to claim 11 wherein the binding component is ~~a chimeric or~~ a CDR-grafted Fab' fragment.

23. (Three times amended) The DNA delivery system according to claim 11 wherein the transmembrane component is the alpha, beta or zeta chain of the T-cell receptor, CD28, CD8, CD4, a cytokine receptor or a colony stimulating factor receptor, or ~~an antigen binding~~ a fragment thereof.

24. (Three times amended) The DNA delivery system according to claim 23 wherein the transmembrane component is ~~derived from all or part of~~ CD28 or a fragment thereof.

28. (Three times amended) The DNA delivery system according to claim 23 wherein the cytoplasmic signalling components comprise CD28 or the zeta chain of the T-cell receptor or ~~an antigen binding~~ a fragment thereof.

31. (Three times amended) The DNA delivery system according to claim ~~52~~ 53 wherein two or more different spacer regions link the binding component ii) and the transmembrane component iii), one region being coded for by said first recombinant DNA construct and the other different region being coded for by said second recombinant DNA construct.

33. (Three times amended) The DNA delivery system according to claim 11 wherein the spacer region is the extracellular region of CD8, CD4 or CD28 or ~~an antigen binding~~ a fragment thereof.

35. (Three times amended) The DNA delivery system according to claim 11 wherein the spacer region is an antibody hinge region or ~~an antigen binding~~ a fragment thereof linked to ~~all or part of~~ the extracellular region of CD28 or a fragment thereof.

~~52~~ 53. (amended) A DNA delivery system according to claim 11, wherein the recombinant DNA construct encodes either the light chain or the heavy chain of said ~~chimeric antibody or~~ CDR-grafted antibody or an antigen binding fragment ~~thereof~~ of said CDR-grafted antibody, said DNA delivery system further comprising a second recombinant DNA construct comprising a promoter operably linked to a reading frame coding for a signal peptide component and the heavy chain or the light chain or said ~~chimeric antibody or~~ CDR-grafted antibody or an antigen binding fragment ~~thereof~~ of said CDR-grafted antibody, such that upon co-expression of said first and second recombinant DNA constructs in the effector cell, the light and heavy chains of the ~~chimeric antibody or~~ CDR-grafted antibody or an antigen binding fragment ~~thereof~~ of said CDR-grafted antibody assemble to form a binding component which binds to a cell surface antigen on a target cell.